-- 23. (New) A recombinant attenuated *Salmonella* cell, which comprises at least one heterologous nucleic acid molecule encoding a *Helicobacter* immunogen, wherein said *Helicobacter* immunogen is a urease, urease subunit or an immunologically reactive fragment thereof and wherein said attenuated cell is capable of expressing said nucleic acid molecule or capable of causing the expression of said nucleic acid molecule in a transformed target cell, and wherein said recombinant attenuated *Salmonella* cell is capable of inducing protective immunity. --

Please cancel claims 2 and 4 without prejudice or disclaimer.

REMARKS

Claims 1-11 and 13-23 are pending in the application. Claims 1, 3, 5-14, 19-20, and 22 have been amended and support for the amendment to Claim 1 may be found on page 2, lines 35-37, of the specification. The remaining claims have been amended for reasons of antecedent basis. New Claim 23 has been added. Claims 2 and 4 have been cancelled. Claim 16 has been withdrawn from consideration and Claims 1-11, 13-15, and 17-22 are rejected.

Applicants thank the Examiner for the courtesy shown to their representative during the telephonic interview of July 8, 2002. It is submitted that the following is an accurate representation of the issues discussed during that interview.

In the Office Action dated March 18, 2002, the Examiner responded to the declaration of Dr. Thomas F. Meyer and stated that it was insufficient to overcome the rejection of Claims 1-11, 13-15, 17, 19-21, and new Claim 22. The Examiner has taken the position that the Declaration is insufficient to overcome a number of the rejections

because the Declaration utilized a strain of Salmonella designated SL3261:YZ222. The Examiner has noted that this strain of Salmonella is not supported by the present specification. The Examiner has also noted that three different promoters were utilized in the Declaration and that only P_{T7} is supported by the specification. Additionally, the Examiner noted that the strains used in the Declaration to immunize a host were not disclosed in the specification. Finally, the Examiner concluded by noting that none of the combinations of expression signals, antigens, and constructs discussed in the Declaration were disclosed in the specification either. As the Declaration allegedly does not disclose data commensurate in scope with the claimed invention, the Examiner maintained her rejections of the claims.

During the interview with the Examiner, it was discovered that the Examiner's rejection was not directed towards the content of the Declaration per se. Rather, the rejection is more directed towards the Declaration not being supported by the specification. In particular, the Examiner has noted that of the promoters discussed in the Declaration, only one, P_{T7}, was mentioned by name in the specification.

The Examiner conceded that the specification does disclose the use of promoters in a broad sense. However, she does not believe that the disclosure is sufficient to encompass P_{phoP} or P_{nirB}. The Examiner has taken the position that P_{phoP} and P_{nirB} are "high-power promoters" and that the generalities used in the specification would not have been sufficient to lead one of ordinary skill to use the promoters discussed in the Declaration.

It is submitted that the use of the P_{phoP} and P_{nirB} promoters in the Declaration is irrelevant to the conclusions of the Declaration and that the positions advanced in the

Declaration are valid based only upon the results obtained from using the P_{T7} promoter. It is submitted that the data generated from the P_{T7} promoter (as seen in the Exhibit B that was attached to the Declaration) is just as good, if not better in some instances, as the data generated from the P_{phoP} and P_{nirB} promoters. Therefore, although the Examiner's position is noted, it is submitted that the Examiner's position is irrelevant in light of the results from P_{T7}. The P_{T7} promoter (which is explicitly disclosed in the specification) clearly shows that the invention functions as claimed and that it is both enabled and superior to the control.

Furthermore, the Examiner's statements show that she believes that the use of P_{phoP} and P_{nirB} promoters should result in significantly better results than the results generated from the use of the P_{T7} promoter. Because the P_{T7} promoter has results that are comparable to, and, in some instances better than, tests using the asserted "high-power promoters" P_{phoP} and P_{nirB}, the Examiner's position that the favorable data in the Declaration was obtained solely due to the use of the P_{phoP} and P_{nirB} promoters is erroneous. On the contrary, the P_{T7} results demonstrate the efficacy of the invention; thus the Examiner's rejection of the Declaration is not well taken. Therefore, the position of the Examiner is herein traversed and it is requested that the objections to the submitted Declaration be withdrawn and that the rejections be removed.

Claims 1-11, 13-15, and 17-22 have been rejected under 35 U.S.C. 112, first paragraph, as not enabled. The Examiner has taken the position that the specification does not enable preventative or therapeutic live vaccines that express any Helicobacter antigen, and compositions which comprise any nucleic acid sequence from Helicobacter as the active agent which is the mimotype or immunogen that is encoded by a nucleic

acid sequence that does not evidence original descriptive support. It is submitted that the Declaration filed on August 22, 2001 sufficiently demonstrates the enablement and efficacy of the claimed invention, as seen with its use of the P_{T7} promoter. Additionally, the use of the additional "high-power" promoters only further demonstrates the efficacy of the claimed invention. Therefore, in light of the amendments made on August 22, 2001 and the declaration, as well as the positions presented above, it is submitted that the rejection is improper and it is requested that the rejection be withdrawn.

Claims 1, 2, 5, and 10 have been rejected under 35 U.S.C. 102(b) as anticipated by Evans (1993) for reasons of record (paper 10, paragraph 16). It is submitted that the amendments made to the claims and that the positions advanced in previous Responses are sufficient to overcome the present rejection. It is observed that the Evans reference used E. Coli and that Salmonella is not disclosed in the Evans reference. Additionally, it is noted that the Examiner's comments regarding the arguments presented in the Response dated August 22, 2001 are not responsive to the arguments presented therein. It is observed that the Examiner's comments are substantial duplicates as those used to respond to the Response dated December 20, 2000. Therefore, as the present invention is limited to Salmonella, it is submitted that the Evans reference does not disclose all of the aspects of the present invention. Therefore, it is submitted that the rejection is clearly improper.

Claims 1-2, 5-6, and 7-10 have been rejected under 35 U.S.C. 102(b) as anticipated by the Odenbreit reference for reasons of record (paper 10, paragraph 17). It is noted that the Odenbreit reference is limited to the use of E. Coli cells and that Salmonella is not disclosed in the reference at all. Additionally, it is noted that the

Examiner's comments regarding the arguments presented in the Response dated August 22, 2001 are not responsive to the arguments presented therein. It is observed that the Examiner's comments are substantial duplicates as those used to respond to the Response dated December 20, 2000. Therefore, as the present application is limited to Salmonella, and because the cited reference does not disclose the use of Salmonella cells, it is submitted that this rejection is improper and it is requested that the rejection be withdrawn.

Claims 1-2, 5, 10, 11, 13, and 17-21 have been rejected under 35 U.S.C. 102(b) as anticipated by the Doidge reference in light of the McKee reference for reasons of record (page 10, paragraph 18). However, it is noted that the Examiner's comments regarding the arguments presented in the Response dated August 22, 2001 are not responsive to the arguments presented therein. It is observed that the Examiner's comments are substantial duplicates as those used to respond to the Response dated December 20, 2000. Therefore, Applicant relies upon the arguments of August 22, 2001 to overcome this rejection and requests that the rejection be withdrawn.

Claims 1, 2, 4, 5, 10, and 17 have been rejected under 35 U.S.C. 102(b) as anticipated by the Dore'-Davin reference for reasons of record (paper 10, paragraph 19). Dore'-Davin is directed towards the use of E. Coli cells and it is observed that Salmonella is not discussed in the Dore'-Davin reference. Therefore, as the present claims are limited to Salmonella, it is submitted that the rejection is improper. Therefore, it is requested that the rejection be withdrawn in light of the amendments made to the claims in this response.

Claims 1-2, 4-5, 10-11, 13-15, and 17-22 have been rejected under 35 U.S.C. 102(b) as anticipated by the Michetti reference for reasons of record (paper 10, paragraph 20). It is submitted that this rejection is not well taken. It is noted that the Michetti reference fails to teach the subject matter of Claim 1. It is observed that the "attenuation" feature of the present claims is mentioned only in Col. 9, line 23, of the Michetti reference. When examined carefully, it can be seen that the possibility of using an attenuated bacterium as a live carrier of urease or other immunogens is not discussed anywhere in the Michetti reference. Therefore, it is submitted that no connection between a carrier for providing the adjuvant and a carrier for expressing the antigen is disclosed in Michetti.

Additionally, the above amendments to Claim 1 also define the present invention over that which is disclosed in the Michetti reference. It is submitted that the Michetti reference does not disclose recombinant attenuated Salmonellae which are capable of protecting vaccinated animals. It is also submitted that the vaccine described in Michetti will not work without an adjuvant. In particular, it is submitted that the Michetti reference does not teach that recombinant Salmonella could achieve protective immunity without an adjuvant. Michetti only teaches that there is no difference in the immunogenic activity of a urease, either expressed in a recombinant live vector or a recombinant carrier system or bound to another carrier, such as hydroxyapatite, together with an adjuvant. Therefore, it is submitted that Michetti is insufficient to anticipate the claimed invention.

Finally, the insufficiency of Michetti is further illustrated by the prior art which teaches that the immunization protocol of Michetti (urease with chloeratoxin B adjuvant)

induces a humoral and cellular type II immune response, while most Salmonallae induce a type I immune response. This was prior art at the publication date of Michetti, and it is the reason why it cannot be concluded from the teachings of the Michetti patent that Salmonella could be used successfully for preparing a live vaccine. Therefore, in light of the above arguments it is requested that the rejection be withdrawn.

Claims 1-11, 13-15, and 17-22 have been rejected under 35 U.S.C. 103(a) as obvious in light of the Michetti patent and the Russell patent for reasons of record (paper 10, paragraph 22). In addition to the above discussion of the Michetti patent, it is submitted that the Russell patent does not teach or suggest a protective live oral vaccine consisting of an attenuated Salmonella carrier that expresses Helicobacter immunogen. Additionally, the disclosure of Russell et al. only provides information regarding humoral responses, and contains no disclosure as to whether a CT A2/B chimeric protein expressed in an attenuated bacterial carrier would induce such a high level of protective immunity after a single oral application. Moreover, Russell et al. uses cholera toxin A2/B, which stimulates a humoral immune response, as an adjuvant. Therefore, it is submitted that the rejection is improper for these reasons as well.

Claims 1-4, and 7-11 have been rejected under 35 U.S.C. 103(a) as obvious in light of the Russell patent and the Bukanov reference for reasons of record (paper 10, paragraph 23).

Russell et al. discloses a method of producing an immune response by oral administration of an attenuated strain of bacteria (e.g. aroA and aroD mutant *Salmonella typhimurium*) wherein said attenuated bacteria expresses an antigen of interest as a cholera toxin A2/B chimeric protein.

Bukanov et al. provide a genetic analysis of a variety of *Helicobacter* genes including virulence factors such as vacA, cagA, ureAB, ureD and ureH.

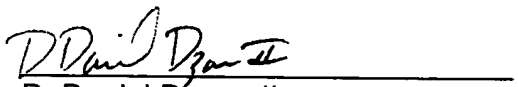
The cited references Russell et al. and Bukanov et al. provide no suggestion or motivation regarding the *Helicobacter* immunogen or live vaccine of the present invention. Russell et al. teaches the expression of cholera toxin A2/B as a fusion protein which has immunogenic properties to induce a humoral response. However, Russell et al. does not teach or suggest an attenuated pathogen comprising a *Helicobacter* immunogen which is capable of inducing protective immunity. Nor does Russell et al. teach or suggest *Helicobacter* immunogens which are expressed in an attenuated bacterial carrier without cholera toxin A2/B as a fusion partner as in the present invention. As noted above, such formulations are capable of inducing protective immunity of about 100% after a single dose application. Applicants note that Bukanov et al. fails to cure any of the deficiencies of Russell et al. It is therefore requested that the rejection be withdrawn for these reasons.

For the foregoing reasons, Applicants' claims now particularly point out and distinctly claim what Applicants regard as their invention in a manner patentably distinguished over all grounds of rejection cited in the Office Action. Accordingly, allowance of all claims 1, 3, 5-11, 13-15, and 17-23 is respectfully requested.

Should the Examiner deem that any further action by the Applicants would be desirable for placing this application in even better condition for issue, the Examiner is requested to telephone applicants' undersigned representative at the number listed below.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referring to client-matter number 100564-09008.

Respectfully submitted,



D. Daniel Dzara, II
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Attachment: Declaration under 37 C.F.R. 1.132

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Attachments: Petition for Extension of Time

MARKED-UP VERSION OF ORIGINAL CLAIMS

1. (Twice Amended) A recombinant attenuated [microbial] *Salmonella* [pathogen]cell, which comprises at least one heterologous nucleic acid molecule encoding a *Helicobacter* immunogen, wherein said attenuated [pathogen] cell is capable of expressing said nucleic acid molecule or capable of causing the expression of said nucleic acid molecule in a transformed target cell, and wherein said [immunogen] recombinant attenuated *Salmonella* cell is capable of inducing protective immunity.

3. (Twice Amended) The [pathogen according to] cell of claim 1, which is a Salmonella aro mutant cell.

5. (Thrice Amended) The [pathogen according to] cell of claim 1, wherein the *Helicobacter* immunogen is secretory polypeptide from *Helicobacter*, an immunologically reactive fragment thereof, or a peptide mimotope thereof.

6. (Thrice Amended) The [pathogen according to] cell of claim 1, wherein the *Helicobacter* immunogen is selected from a group consisting of the antigens adherance-associated lipoprotein A (AlpA), adherance-associated lipoprotein B (AlpB), immunologically reactive fragments thereof, or a peptide mimotope thereof.

7. (Thrice Amended) The [pathogen according to] cell of claim 1, wherein said nucleic acid molecule encoding a *Heliobacter* immunogen is capable to be expressed phase variably.

8. The [pathogen according to] cell of claim 7, wherein said nucleic acid molecule encoding the *Helicobacter* immunogen is under control of an expression signal which is substantially inactive in the pathogen and which is capable to be activated by a

nucleic acid reorganization caused by a nucleic acid reorganization mechanism in the pathogen.

9. (Once Amended) The [pathogen according to] cell of claim 8, wherein the expression signal is a bacteriophage promoter, and the activation is caused by a DNA reorganization resulting in the production of a corresponding bacteriophage RNA polymerase in the pathogen.

10. (Twice Amended) The [pathogen according to] cell of claim 1, further comprising at least one second nucleic acid molecule encoding an immunomodulary polypeptide, wherein said pathogen is capable to express said second nucleic acid molecule.

11. (Thrice Amended) Pharmaceutical composition comprising as an active agent a recombinant attenuated [pathogen] cell according to claim 1, together with a pharmaceutically acceptable diluent, carrier or adjuvant.

13. (Thrice Amended) A method for the preparation of a living vaccine comprising providing the [attenuated pathogen] cell of claim 1 and formulating the [attenuated pathogen] cell in a pharmaceutically effective amount for inducing protective immunity with pharmaceutically acceptable diluents, carriers or adjuvants.

14. (Twice Amended) A method for preparing a recombinant attenuated [pathogen] cell according to claim 1, comprising the steps:

a) inserting a nucleic acid molecule encoding a *Helicobacter* immunogen into an attenuated [pathogen] Salmonella cell, wherein a recombinant attenuated [pathogen] Salmonella cell is obtained, which is capable of expressing said nucleic acid molecule or is capable to cause expression of said nucleic acid molecule in a target cell, and

b) cultivating said recombinant attenuated [pathogen] Salmonella cell under suitable conditions.

19. (Once Amended) A method of treating an infection by *Helicobacter pylori*, comprising administering to a patient in need thereof a composition comprising the [attenuated pathogen] cell of claim 1 in a pharmaceutically effective amount for inducing protective immunity.

20. (Once Amended) A method of preventing an infection by *Helicobacter pylori*, comprising administering to a patient a composition comprising the [attenuated pathogen] cell of claim 1 in a pharmaceutically effective amount for inducing protective immunity.

22. (Once Amended) A method of inducing protective immunity against a *Helicobacter* infection in a mammalian host comprising administering to a mammalian host in need of protective immunity an effective amount of the cell of claim 1.